257. *Walden Inversion in the Glucose Series. Derivatives of Altrose.*

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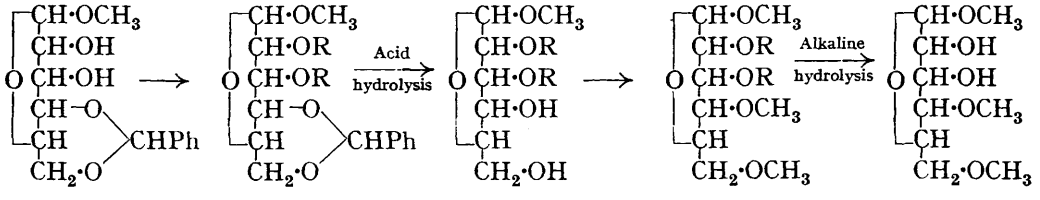
The exact means by which Nature effects fundamental transformations in the sugar group remains shrouded in obscurity, but a little light has been thrown on the subject by Robinson (*Nature*, 1927, **120**, 44), whose conception of Walden inversion within the sugar molecule gives a rational explanation of such changes as the interconversion of isomeric sugars. The conversion of glucose into galactose by the mammary glands during lactation is thus attributed to a Walden inversion on carbon atom number 4, which is conditioned by the enzymatic hydrolysis of a glucose-4-phosphoric acid. Direct experimental corroboration of this hypothesis is lacking, but it is strongly supported by the results now communicated. We have succeeded in transforming a derivative of glucose smoothly and in one operation into a derivative of altrose. It is not yet clear how far our method is of general application, but the whole problem is being explored in this laboratory.

The suitability of the 4 : 6-benzylidene methylglucosides as starting points in the synthesis of partially methylated glucoses was first demonstrated by Irvine and Scott (J., 1913, **103**, 585) in their synthesis of 2 : 3-dimethyl glucose. It was considered desirable to extend this work to the preparation of 4 : 6-dimethyl glucose. The general line of approaching the problem is illustrated in the following scheme.

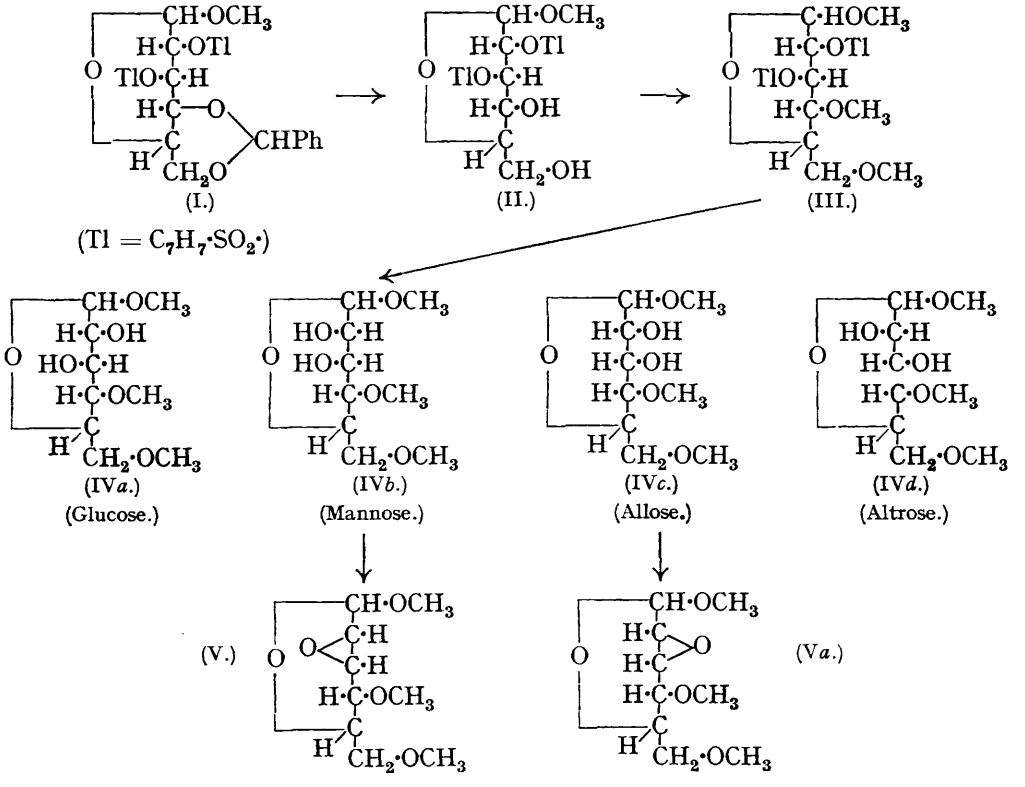


The main difficulty in this apparently straightforward process lies in the discovery of a substituent which will act as a temporary but adequate protection for the hydroxyl groups in positions 2 and 3. The acetyl group cannot be used for this purpose because of complications which ensue through catalytic migration of the acetyl groups during the subsequent methylation. For the same reason, it was considered doubtful if the use of the benzoyl group would prove satisfactory, and this doubt was fully substantiated by experiment. 2 : 3-Dibenzoyl 4 : 6-benzylidene α-methylglucoside is a crystalline substance which, on partial hydrolysis, yields 2 : 3-*dibenzoyl α-methylglucoside* as a clear golden-yellow glass. The methylation of this substance was accompanied by a serious loss in benzoyl content. The impure 2 : 3-*dibenzoyl* 4 : 6-*dimethyl α-methylglucoside* was submitted to alkaline hydrolysis, precautions being taken to eliminate unchanged material, and also tetra- or penta-methyl glucoses, which might have originated through the loss of benzoyl groups and subsequent methylation of the hydroxyl groups thus exposed. A syrup was isolated which had the empirical composition of a dimethyl methylglucoside. This syrup was condensed with *p*-toluenesulphonyl chloride and crystalline 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside was isolated in 54% yield. From this

result, it is apparent that although 4 : 6-dimethyl α-methylglucoside is present to the extent of 54%, the final product is a mixture of isomeric dimethyl α-methylglucosides. In all probability the loss of benzoyl content during methylation is accompanied by catalytic migration of the benzoyl groups.

In a subsequent series of experiments, *p*-nitrobenzoyl chloride was used in place of benzoyl chloride in condensations with 4 : 6-benzylidene α-methylglucoside. 2 : 3-*Di*-p-*nitrobenzoyl* 4 : 6-*benzylidene* α-*methylglucoside* is a crystalline substance which gives a crystalline 2 : 3-*di*-p-*nitrobenzoyl* α-*methylglucoside* on partial hydrolysis. The methylation of this substance was, however, attended by complications similar to those described in the case of the analogous dibenzoyl derivative, and the investigation was abandoned.

A third series of experiments, in which the hydroxyl groups in positions 2 and 3 were protected by means of condensation with *p*-toluenesulphonyl chloride, gave unexpected results. When 2 : 3-di-*p*-toluenesulphonyl 4 : 6-benzylidene α-methylglucoside (I) (Ohle and Spencker, *Ber.*, 1928, **61**, 2387; Mathers and Robertson, this vol., p. 696) was submitted to gentle hydrolysis, the benzylidene residue was readily removed, with the production of 2 : 3-*di*-p-*toluenesulphonyl* α-*methylglucoside* (II), which could not be obtained in a crystalline state but was readily converted into crystalline 2 : 3-*di*-p-*toluenesulphonyl* 4 : 6-*dimethyl* α-*methylglucoside* (III), in almost theoretical yield. The yield of this compound is important, as it excludes the possibility of *p*-toluenesulphonyl rearrangement during the methylation.



The alkaline hydrolysis of 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside followed an unexpected course, and two distinct products were isolated: a crystalline dimethyl anhydromethylhexoside, (A), in 66% yield, and a syrup, (B), which had the empirical composition of a dimethyl methylhexoside, in 26% yield. Part of the syrup (B), which was expected to consist essentially of 4 : 6-dimethyl α-methylglucoside, (IV*a*), was recondensed with *p*-toluenesulphonyl chloride and yielded a crystalline di-*p*-toluenesulphonyl derivative in 75% yield, which, however, was not identical with the starting material,

2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside (III). If the possibility of the migration of methyl groups is discounted, the production of this isomeric di-*p*-toluenesulphonyl derivative may only be explained on the assumption that a Walden inversion has taken place during the alkaline hydrolysis of the original ester, with the consequent production of a derivative of an isomeric hexose. The work of Phillips (J., 1923, **123**, 44; 1925, **127**, 399), who has shown that the alkaline hydrolysis of *p*-toluenesulphonic esters may be accompanied by almost complete Walden inversion, supplies good confirmatory evidence for this view.

In the case under discussion, two *p*-toluenesulphonyl residues are involved in the hydrolysis, from which it follows that inversion may occur at position 2 or 3 or at both. Three configurations therefore come under consideration, (IV*b*), (IV*c*), and (IV*d*); *i.e.*, the syrup, (B), consists essentially of a derivative of mannose, allose, or altrose. The possibility of a mixture is to a large extent excluded by the yield of the new isomeric di-*p*-toluenesulphonyl derivative. Further evidence was obtained by submitting the syrup, (B), to methylation, whereupon a syrup corresponding with a tetramethyl methylhexoside was isolated. The fully methylated substance showed $[\alpha]_D + 145{\cdot}6°$ in absolute alcohol. Tetramethyl α-methylmannoside shows $[\alpha]_D + 75{\cdot}5°$ in the same solvent. Hydrolysis of the glucosidic methyl group yielded a syrup which partially crystallised, and from which a crystalline tetramethyl hexose was isolated in small amount. The new sugar melted at 76—78° and showed $[\alpha]_D + 97{\cdot}4°$ in absolute alcohol. Tetramethyl mannose is a syrup and is almost inactive, but the above physical constants indicated tetramethyl glucose, an idea which was definitely disproved by the fact that a mixture of the new sugar derivative with an authentic specimen of tetramethyl glucose (m. p. 82°) melted at 65—70°. Glucose and mannose may therefore be dismissed from consideration, and of the remaining possibilities the altrose configuration is preferred for reasons which are developed below. The crystalline di-*p*-toluenesulphonyl derivative is tentatively described as 2 : 3-*di*-p-*toluenesulphonyl* 4 : 6-*dimethyl α-methylaltroside*, and the tetramethyl hexose as 2 : 3 : 4 : 6-*tetramethyl altrose*.

The crystalline product of alkaline hydrolysis, (A), was proved by analysis to correspond with a dimethyl anhydromethylhexoside. This was confirmed by the fact that when submitted to repeated methylation it was recovered entirely unchanged. Moreover, it reacted neither with acetic anhydride nor with *p*-toluenesulphonyl chloride. When the complication due to the Walden inversion is admitted, it becomes clear that this anhydro-compound may be related to any one of the four configurations indexed as (IV*a*), (IV*b*), (IV*c*), and (IV*d*). The anhydro-linkage is obviously between positions 2 and 3, and is therefore of the ethylene oxide type. From a consideration of the strain involved in such a linkage, it is reasonable to suggest that the elimination of the elements of water is much more likely to take place in the cases in which the hydroxyl groups in question are in the *cis*-position, *i.e.*, anhydro-formation is more probable in cases (IV*b*) and (IV*c*). It follows that the substance under discussion is either 4 : 6-*dimethyl* 2 : 3-*anhydro-α-methyl-mannoside* (V) or *-alloside* (V*a*). This argument may also be used to emphasise our preference for the altrose configuration proposed for the crystalline substances derived from the syrup (B). Our previous argument narrowed the choice to allose and altrose, but since anhydro-formation has also been proved to take place during the reaction, it seems probable that if the allose configuration were produced it would immediately undergo dehydration to give the anhydro-derivative.

It is now possible to suggest a mechanism for the alkaline hydrolysis of 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside which is in harmony with the argument developed above. Hydrolysis of the *p*-toluenesulphonyl groups is accompanied by a complete inversion of hydrogen and hydroxyl on carbon atom number 2, simultaneously with a partial inversion on carbon atom 3, so that a mixture of derivatives of mannose and altrose results. The mannose derivative immediately undergoes dehydration to give an anhydro-compound, while the altrose derivative, in which the hydroxyl groups are in the *trans*-position, is unaffected. The preponderance of the anhydro-compound over the simple sugar derivative may be quoted as confirmation of this view. It is recognised, however, that an alternative explanation does exist. Complete inversion on carbon

atom 3 accompanied by partial inversion on carbon atom 2 leads to similar results, with the essential difference that the anhydro-compound becomes a derivative of allose. Further research is necessary before a definite configuration can be ascribed to this crystalline dimethyl anhydro-methylhexoside.

Experimental.

2 : 3-Dibenzoyl **4 : 6**-benzylidene α-methylglucoside was prepared by a variation of the method due to Ohle and Spencker (*Ber.*, 1928, **61**, 2392; cf. Mathers and Robertson, *loc. cit.*).

2 : 3-*Dibenzoyl* α-*Methylglucoside.*—**2 : 3**-Dibenzoyl **4 : 6**-benzylidene α-methylglucoside (10 g.) was dissolved in acetone (200 c.c.) containing 0·25% hydrogen chloride, and the solution boiled until the rotation became constant (6½ hours) : $[\alpha]_D$ + 150·1° (calculated on weight of starting material), or + 183° (calculated on theoretical amount of dibenzoyl α-methylglucoside formed). The solution was neutralised with barium carbonate, the acetone and liberated benzaldehyde were removed by distillation in steam, and the residue was thoroughly extracted with chloroform. After drying (sodium sulphate) and removal of the solvent, **2 : 3**-*dibenzoyl* α-*methylglucoside* was obtained as a yellow glass in theoretical yield. It was insoluble in light petroleum, but easily soluble in ether, acetone, benzene, and chloroform. It showed $[\alpha]_D$ + 154·4° (c = 1·202 in absolute alcohol); + 102·5° (c = 2·966 in chloroform) (Found : OCH_3, 7·2; $C_6H_5{\cdot}CO$, 53·7. $C_{21}H_{22}O_8$ requires OCH_3, 7·7; $C_6H_5{\cdot}CO$, 52·2%).

Methylation of **2 : 3**-*Dibenzoyl* α-*Methylglucoside.*—The material obtained above was methylated in the usual way with methyl iodide and silver oxide. One methylation raised the methoxyl content to 17·3% ($C_{23}H_{26}O_8$ requires OCH_3, 21·6%), and three further methylations raised it to 20·5%, but a benzoyl estimation on the product thus obtained gave the value 43·3% (Calc. : 48·8%). Methylation is therefore accompanied by a partial displacement of benzoyl groups, and the impure product, which was a yellow glass, could not be crystallised.

Alkaline Hydrolysis of Impure **2 : 3**-*Dibenzoyl* **4 : 6**-*Dimethyl* α-*Methylglucoside.*—The material (14·2 g.) was dissolved in alcohol (190 c.c.) and an equal volume of 0·5N-potassium hydroxide was gradually added to the boiling solution. After 3 hours' boiling, the alcohol was removed by distillation under diminished pressure, and the residue just acidified with hydrochloric acid, then neutralised with barium carbonate. After filtration, the solution was thoroughly extracted with chloroform. The extract yielded a brown gum (2·3 g.), which consisted of unhydrolysed material together with any trimethyl and tetramethyl α-methylglucosides which may have resulted through the loss of benzoyl content during the methylation. The aqueous solution was now evaporated to dryness, and the residue extracted with boiling chloroform. This extract yielded a thick syrup (4·5 g.; 61%) which was distilled in a vacuum; b. p. 155° (bath temperature)/0·03 mm. This colourless viscous syrup, which had n_D 1·4731, $[\alpha]_D$ + 165·7° (c = 1·865 in chloroform), neither reduced Fehling's solution nor decolorised a solution of bromine in carbon tetrachloride (Found : OCH_3, 39·5. $C_9H_{18}O_6$ requires OCH_3, 41·9%). Part of this syrup (1·4 g.) was condensed with p-toluenesulphonyl chloride in pyridine (Ohle, *loc. cit.*), and yielded a yellow gum (3·0 g.; 90%), which slowly crystallised on treatment with methyl alcohol. The yield of crystalline material was 1·8 g. (54%). It had m. p. 113—115° $[\alpha]_D$ + 55·0° (c = 2·689 in chloroform); a mixture with **2 : 3**-di-p-toluenesulphonyl **4 : 6**-dimethyl α-methylglucoside, m. p. 116—117°, melted at 114—116°. The final product therefore contains at least 54% of **4 : 6**-dimethyl α-methylglucoside. It is probable that the remainder consists of isomeric sugars formed by the catalytic rearrangement of benzoyl groups during the methylation.

2 : 3-*Di*-p-*nitrobenzoyl* **4 : 6**-*Benzylidene* α-*Methylglucoside.*—Benzylidene α-methylglucoside (5·2 g.) was dissolved in pyridine (10 c.c.), and a solution of p-nitrobenzoyl chloride (10·3 g.) in chloroform added gradually. After 4 days, more chloroform was added, and the solution was washed with dilute hydrochloric acid, dilute sodium carbonate solution, and finally with water; after drying (sodium sulphate) and removal of the solvent, it yielded 9·0 g. (85%) of crystalline material, m. p. 165—167°. Crystallisation from alcohol–chloroform (10 : 1) raised the m. p. to 169—170°. **2 : 3**-*Di*-p-*nitrobenzoyl* **4 : 6**-*benzylidene* α-*methylglucoside* crystallises in colourless needles, $[\alpha]_D$ + 127·7° (c = 2·635 in chloroform) (Found : OCH_3, 5·37. $C_{28}H_{24}O_{12}N_2$ requires OCH_3, 5·35%).

2 : 3-*Di*-p-*nitrobenzoyl* α-*Methylglucoside.*—The removal of the benzylidene residue was effected in the manner described for the analogous dibenzoyl derivative. 10·0 G. of starting material gave 8·5 g. of a hard glass which crystallised from alcohol in white needles, m. p. 143—155°, not sharp after recrystallisation (Found : OCH_3, 6·25. $C_{21}H_{20}O_{12}N_2$ requires OCH_3, 6·30%).

Methylation of this *glucoside* in the usual way gave a product which contained 18·4% of methoxyl as compared with a theoretical value of 17·9%. A second methylation raised the methoxyl content to 20·5%.

2 : 3-Di-*p*-toluenesulphonyl 4 : 6-benzylidene α-methylglucoside was prepared by a variation of the method due to Ohle (*loc. cit.*). The benzylidene residue was removed as described for the corresponding dibenzoate, and 2 : 3-*di*-p-*toluenesulphonyl* α-*methylglucoside* was obtained in theoretical yield as an uncrystallisable glass; $[\alpha]_D$ + 58·5° (*c* = 3·026 in chloroform) (Found : OCH_3, 6·36. $C_{21}H_{26}O_{10}S_2$ requires OCH_3, 6·2%). Methylation with methyl iodide and silver oxide gave a theoretical yield of 2 : 3-*di*-p-*toluenesulphonyl* 4 : 6-*dimethyl* α-*methylglucoside*; colourless needles, m. p. 116—117°, from methyl alcohol; $[\alpha]_D$ + 54·7° (*c* = 3·027 in chloroform); + 63·8° (*c* = 1·538 in acetone) (Found : OCH_3, 17·2. $C_{23}H_{30}O_{10}S_2$ requires OCH_3, 17·55%).

Alkaline Hydrolysis of 2 : 3-*Di*-p-*toluenesulphonyl* 4 : 6-*Dimethyl* α-*Methylglucoside.*—The crystalline material (50 g.) was dissolved in hot alcohol containing an equal volume of 2*N*-potassium hydroxide, and the solution was boiled for 3 hours. A dark brown coloration rapidly developed, and it was impossible to follow the reaction polarimetrically. The cooled solution was neutralised with sulphuric acid and evaporated to dryness under low pressure. The residue was thoroughly extracted with hot chloroform, and removal of the solvent from the filtered extract yielded a syrup (29 g.); this was again dissolved in chloroform, and the solution thoroughly extracted with water. The aqueous extract yielded a syrup (5·5 g.); the chloroform solution was again evaporated to dryness, the residue was dissolved in benzene, and the solution thoroughly extracted with water. This extract yielded a syrup (A), which crystallised spontaneously (9 g.). The benzene solution was now found to contain unchanged 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside (11·1 g.).

The syrup (5·5 g.) was distilled in a vacuum. A small first fraction (1 g.), b. p. 121—130° (bath temperature)/0·8 mm., crystallised in the receiver, and proved to be identical with the crystalline material mentioned above. The remainder distilled at 150—155° (bath temperature)/0·8 mm. and formed a colourless syrup, (B) (4·2 g.). The material (A) proved to be a dimethyl anhydro-methylhexoside, and (B) to have the empirical composition of a dimethyl methylhexoside. The yields of (A) and (B) calculated on the basis of 39 g. of starting material are approx. 66% and 26% respectively.

Examination of the Syrup (*B*).—This *substance* had n_D 1·4730, $[\alpha]_D$ + 138·9° (*c* = 2·225 in water) (Found : OCH_3, 41·1. $C_9H_{18}O_6$ requires OCH_3, 41·9%); it did not reduce Fehling's solution nor did it decolorise a solution of bromine in carbon tetrachloride. Part of the syrup (1 g.) was condensed with *p*-toluenesulphonyl chloride in the usual way. The product was a glass (2·2 g.; 92%) which slowly crystallised. Recrystallisation from methyl alcohol gave 1·8 g. (75%) of a crystalline 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylhexoside, m. p. 132—134°, $[\alpha]_D$ + 103·3° (*c* = 1·133 in chloroform). On admixture with 2 : 3-di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside, m. p. 116°, the m. p. was depressed to 101—105° (Found : OCH_3, 17·36. $C_{23}H_{30}O_{10}S_2$ requires OCH_3, 17·55%). The new substance is considered to be 2 : 3-*di*-p-*toluenesulphonyl* 4 : 6-*dimethyl* α-*methylaltroside.*

Methylation of the Syrup (*B*).—The syrup (2 g.) was methylated with methyl iodide and silver oxide. After three treatments, the product (2 g.) had n_D 1·4476 and a methoxyl content of 58·7% as compared with n_D 1·4464 and 62% for tetramethyl methylglucoside. The low methoxyl content is without doubt due to the presence of slight traces of the anhydro-derivative from which it was separated. The fully methylated syrup showed $[\alpha]_D$ + 145·6° (*c* = 5·013 in alcohol) (cf. tetramethyl α-methylmannoside, which shows $[\alpha]_D$ + 75·5° in alcohol; Irvine and Moodie, J., 1905, **87**, 1467). Hydrolysis of the glucosidic methyl group was effected by boiling with 7% hydrochloric acid until the rotation became constant; 1·5 g. yielded 1·4 g. of a colourless mobile syrup, $[\alpha]_D$ + 65° (*c* = 4·014 in alcohol). On standing, this syrup partially crystallised and the mixture was pressed on a porous tile. In this way, 0·1 g. of clean crystals was obtained, which melted sharply at 76—78°, and had $[\alpha]_D$ + 97·4° (*c* = 0·770 in alcohol) (Found : OCH_3, 51·1. $C_{10}H_{20}O_6$ requires OCH_3, 52·5%). When mixed with an authentic specimen of tetramethyl glucose, m. p. 82°, it melted at 65—70°. The tile was powdered and extracted with ether, and the syrup thus recovered again partly crystallised. The new sugar is believed to be 2 : 3 : 4 : 6-*tetramethyl* α-*methylaltrose.*

Examination of the Crystalline Material (*A*).—The material (10 g.) was distilled in a vacuum and crystallised immediately in the receiver. It appeared still to be contaminated with traces of the syrup (B), and was therefore crystallised from light petroleum. The pure substance separated in long colourless needles, m. p. 63—64°, $[\alpha]_D$ + 188·9° (*c* = 1·017 in chloroform).

It neither reduced Fehling's solution nor decolorised a solution of bromine in carbon tetrachloride. Analysis proved that it was a *dimethyl anhydro-α-methylhexoside* (Found: OCH_3, 43·6; C, 52·6; H, 7·7. $C_9H_{16}O_5$ requires OCH_3, 45·6; C, 52·9; H, 7·9%).

An attempt to methylate the purified substance (2 g.) by means of methyl iodide and silver oxide failed, the original material being recovered quantitatively unchanged after three treatments. The purified material (0·5 g.) was dissolved in pyridine and treated with acetic anhydride (0·7 c.c.). After standing for two days, the mixture was dissolved in benzene and thoroughly washed with water, but the benzene layer yielded nothing on evaporation.

The purified crystals (0·15 g.) were treated with *p*-tolunesulphonyl chloride (0·4 g.) in pyridine solution. After four days, the mixture, which had become pale yellow, was dissolved in benzene, and the solution washed with water. The washings showed optical activity which corresponded with 0·13 g. of starting material, but the benzene layer was practically inactive. The configuration of this 4 : 6-dimethyl 2 : 3-anhydro-α-methylhexoside is still uncertain.

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